

CLAIMS

What is claimed is:

1. A method for preparing submicron sized particles of an organic compound, the solubility of which is greater in a water-miscible first solvent than in a second solvent which is aqueous, the process comprising the steps of:

(i) dissolving the organic compound in the water-miscible first solvent to form a solution, the first solvent being selected from the group consisting of N-methyl-2-pyrrolidinone, 2-pyrrolidone, dimethyl sulfoxide, dimethylacetamide, lactic acid, methanol, ethanol, isopropanol, 3-pentanol, n-propanol, glycerol, butylene glycol, ethylene glycol, propylene glycol, mono- and diacylated monoglycerides, dimethyl isosorbide, acetone, dimethylformamide, 1,4-dioxane, polyethylene glycol, polyethylene glycol esters, polyethylene glycol sorbitans, polyethylene glycol monoalkyl ethers, polypropylene glycol, polypropylene alginate, PPG-10 butanediol, PPG-10 methyl glucose ether, PPG-20 methyl glucose ether, PPG-15 stearyl ether, propylene glycol dicaprylate, propylene glycol dicaprinate, propylene glycol laurate;

(ii) mixing the solution with the second solvent to define a pre-suspension of particles in a friable form; and

(iii) adding energy to the pre-suspension to form particles having an average effective particle size of from about 400 nm to about 2 micron.

2. The method of claim 1 further comprising the step of:
mixing into the second solvent a first surface modifier selected from the group consisting of: anionic surfactants, cationic surfactants and nonionic surfactants.

3. The method of claim 2 wherein the nonionic surfactant is selected from the group consisting of: polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, polyvinylpyrrolidone, albumin, heparin, and hirudin.

4. The method of claim 2 wherein the anionic surfactant is selected from the group consisting of: potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl glycerol, phosphatidyl inositol, phosphatidylserine,

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6. The method of claim 2 wherein the first solvent is N-methyl-2-pyrrolidinone.

10 7. The method of claim 6 wherein the anionic surfactant is a copolymer of oxyethylene and oxypropylene.

8. The method of claim 7 wherein the copolymer of oxyethylene and oxypropylene is a block copolymer.

9. The method of claim 2 further comprising the step of mixing into the
15 second solvent a second surface modifier.

10. The method of claim 9 wherein the second surface modifier is selected from the group consisting of anionic surfactants, cationic surfactants and nonionic surfactants.

11. The method of claim 10 wherein the second surface modifier is a bile salt or a salt thereof.

12. The method of claim 10 wherein the second surface modifier is selected from deoxycholic acid, glycocholic acid, glycodeoxycholic acid, taurocholic acid and salts of these acids.

13. The method of claim 2 further comprising the step of adding a pH
25 adjusting agent to the second solvent.

14. The method of claim 13 wherein the pH adjusting agent is selected from the group consisting of sodium hydroxide, hydrochloric acid, tris buffer, citrate buffer, acetate, lactate, and meglumine.

15. The method of claim 13 wherein the pH adjusting agent is added to the
30 second solvent to bring the pH of the second solvent within the range of from about 3 to
about 11.

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16. The method of claim 1 further comprising the step of:
mixing into the solution a third surface modifier selected from the group

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consisting of: anionic surfactants, cationic surfactants and nonionic surfactants.

17. The method of claim 16 wherein the nonionic surfactant of the third surface modifier is selected from the group consisting of: polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxypropylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

18. The method of claim 16 wherein the anionic surfactant of the third surface modifier is selected from the group consisting of: potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl glycerol, phosphatidyl inositol, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, bile acids and their salts and calcium carboxymethylcellulose.

19. The method of claim 16 wherein the cationic surfactant of the third surface modifier is selected from the group consisting of quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride.

20 20. The method of claim 16 wherein the first solvent is N-methyl-2-
pyrrolidinone.

21. The method of claim 20 wherein the third surface modifier is a copolymer of oxyethylene and oxypropylene.

22. The method of claim 21 wherein the copolymer of oxyethylene and
oxypropylene is a block copolymer.

23. The method of claim 16 further comprising the step of mixing into the solution a fourth surface modifier.

24. The method of claim 23 wherein the fourth surface modifier is selected from the group consisting of: anionic surfactants, cationic surfactants and nonionic surfactants.

25. The method of claim 24 wherein the fourth surface modifier is a nonionic surfactant selected from the group consisting of: polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol

monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

5 26. The method of claim 24 wherein the fourth surface modifier is a nonionic surfactant selected from the group consisting of: polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

10 27. The method of claim 24 wherein the fourth surface modifier is a cationic surfactant selected from the group consisting of: of quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride.

15 28. The method of claim 16 further comprising the step of:
mixing into the second solvent a fifth surface modifier selected from the group consisting of: anionic surfactants, cationic surfactants and nonionic surfactants.

20 29. The method of claim 28 wherein the fifth surface modifier is a nonionic surfactant selected from the group consisting of: polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

25 30. The method of claim 28 wherein the fifth surface modifier is an anionic surfactant selected from the group consisting of: potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl glycerol, phosphatidyl inositol, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, bile acids and their salts and calcium carboxymethylcellulose.

30 31. The method of claim 28 wherein the fifth surface modifier is a cationic surfactant selected from the group consisting of quaternary ammonium compounds,

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benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride.

32. The method of claim 28 wherein the first solvent is N-methyl-2-pyrrolidinone.

5 33. The method of claim 32 wherein the fifth surface modifier is a copolymer of oxyethylene and oxypropylene.

34. The method of claim 33 wherein the copolymer of oxyethylene and oxypropylene is a block copolymer.

6 35. The method of claim 28 further comprising the step of mixing into the solution a sixth surface modifier selected from the group consisting of: anionic surfactants, cationic surfactants and nonionic surfactants.

36. The method of claim 1 further comprising the step of:
mixing into the second solvent a phospholipid.

15 37. The method of claim 36 wherein the phospholipid is selected from natural phospholipids and synthetic phospholipids.

38. The method of claim 36 wherein the phospholipid is selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, egg phospholipid and soybean phospholipid.

7 39. The method of claim 36 further comprising the step of mixing into the solution a seventh surface modifier selected from anionic surfactants, cationic surfactants and non-ionic surfactants.

40. The method of claim 39 wherein the nonionic surfactant of the seventh surface modifier is selected from the group consisting of: polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

41. The method of claim 39 wherein the anionic surfactant of the seventh surface modifier is selected from the group consisting of: potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl

glycerol, phosphatidyl inositol, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, bile acids and their salts and calcium carboxymethylcellulose.

5 42. The method of claim 39 wherein the cationic surfactant of the seventh surface modifier is selected from the group consisting of quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride.

10 43. The method of claim 39 wherein the seventh surface modifier is a bile acid or a salt thereof.

10 44. The method of claim 39 wherein the first solvent is N-methyl-2-pyrrolidinone.

45. The method of claim 44 further comprising the step of adding a phospholipid to the second solvent.

15 46. The method of claim 45 wherein the phospholipid is selected from natural phospholipids and synthetic phospholipids.

47. The method of claim 45 wherein the phospholipid is selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, egg phospholipid and soybean phospholipid.

20 48. The method of claim 45 further comprising the step of mixing into the solution an eighth surface modifier selected from anionic surfactants, cationic surfactants and non-ionic surfactants.

25 49. The method of claim 48 wherein the nonionic surfactant of the eighth surface modifier is selected from the group consisting of: polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

30 50. The method of claim 48 wherein the anionic surfactant of the eighth surface modifier is selected from the group consisting of: potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl

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glycerol, phosphatidyl inositol, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, bile acids and their salts and calcium carboxymethylcellulose.

5 51. The method of claim 48 wherein the cationic surfactant of the eighth surface modifier is selected from the group consisting of quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride.

52. The method of claim 48 wherein the eighth surface modifier is a bile acid or a salt thereof.

10 53. The method of claim 48 wherein the first solvent is N-methyl-2-pyrrolidinone.

54. A method for preparing submicron sized particles of an organic compound, the solubility of which is greater in a water-miscible first solvent than in a second solvent which is aqueous, the process comprising the steps of:

15 (i) dissolving the organic compound in the water-miscible first solvent to form a solution, the first solvent being selected from the group consisting of N-methyl-2-pyrrolidinone, 2-pyrrolidone, dimethyl sulfoxide, dimethylacetamide, lactic acid, methanol, ethanol, isopropanol, 3-pentanol, n-propanol, glycerol, butylene glycol, ethylene glycol, propylene glycol, mono- and diacylated monoglycerides, dimethyl
20 isosorbide, acetone, dimethylformamide, 1,4-dioxane, polyethylene glycol, polyethylene glycol esters, polyethylene glycol sorbitans, polyethylene glycol monoalkyl ethers, polypropylene glycol, polypropylene alginate, PPG-10 butanediol, PPG-10 methyl glucose ether, PPG-20 methyl glucose ether, PPG-15 stearyl ether, propylene glycol dicaprylate, propylene glycol dicaprate, propylene glycol laurate;

25 (ii) mixing into the second solvent a first surface modifier selected from the group consisting of: anionic surfactants, cationic surfactants and nonionic surfactants;

(iii) mixing the solution with the second solvent and first surface modifier to define a pre-suspension of particles in a friable form; and

30 (iv) adding energy to the pre-suspension to form particles having an average effective particle size of from about 400 nm to about 2 microns.

55. The method of claim 54 wherein the nonionic surfactant is selected from the group consisting of: polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene

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glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

5 56. The method of claim 54 wherein the anionic surfactant is selected from the group consisting of: potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl glycerol, phosphatidyl inositol, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, bile
10 acids and their salts and calcium carboxymethylcellulose.

57. The method of claim 54 wherein the cationic surfactant is selected from the group consisting of quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride.

15 58. The method of claim 54 wherein the first solvent is N-methyl-2-pyrrolidinone.

59. The method of claim 58 wherein the anionic surfactant is a copolymer of oxyethylene and oxypropylene.

60. The method of claim 59 wherein the copolymer of oxyethylene and oxypropylene is a block copolymer.

61. The method of claim 54 further comprising the step of mixing into the second solvent a second surface modifier.

20 62. The method of claim 61 wherein the second surface modifier is selected from the group consisting of anionic surfactants, cationic surfactants and nonionic surfactants.
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63. The method of claim 62 wherein the second surface modifier is selected from bile acids and salts thereof.

64. The method of claim 54 further comprising the step of adding a pH adjusting agent to the second solvent.

30 65. The method of claim 64 wherein the pH adjusting agent is selected from the group consisting of sodium hydroxide, hydrochloric acid, citrate buffer, acetate, lactate, and meglumine.

66. The method of claim 64 wherein the pH adjusting agent is added to the

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second solvent to bring the pH of the second solvent within the range of from about 4 to about 10.

67. The method of claim 54 wherein the energy-addition step comprises the step of:

5 subjecting the pre-suspension to heating, sonication, homogenization, counter current flow homogenization or microfluidization.

68. The method of claim 67 wherein the energy-addition step further comprises the step of subjecting the pre-suspension to heat.

69. The method of claim 54 further comprising the step of removing solvent
10 and excess surfactants.

70. The method of claim 69 wherein the solvent and surfactant removal step is accomplished via centrifugation, diafiltration, force-field fractionation, or high-pressure filtration.

71. A method for preparing submicron sized particles of an organic
15 compound, the solubility of which is greater in a water-miscible first solvent than in a second solvent which is aqueous, the process comprising the steps of:

(i) dissolving the organic compound in the water-miscible first
solvent to form a solution, the first solvent being selected from the group consisting of N-methyl-2-pyrrolidinone, 2-pyrrolidone, dimethyl sulfoxide, dimethylacetamide, lactic
20 acid, methanol, ethanol, isopropanol, 3-pentanol, n-propanol, glycerol, butylene glycol, ethylene glycol, propylene glycol, mono- and diacylated monoglycerides, dimethyl isosorbide, acetone, dimethylformamide, 1,4-dioxane, polyethylene glycol, polyethylene glycol esters, polyethylene glycol sorbitans, polyethylene glycol monoalkyl ethers, polypropylene glycol, polypropylene alginate, PPG-10 butanediol, PPG-10 methyl
25 glucose ether, PPG-20 methyl glucose ether, PPG-15 stearyl ether, propylene glycol dicaprylate, propylene glycol dicaprate, propylene glycol laurate;

(ii) mixing into the solution a first surface modifier selected from the group consisting of: anionic surfactants, cationic surfactants and nonionic surfactants;

(iii) mixing the solution and first surface modifier with the second
30 solvent to define a pre-suspension of particles in a friable form; and

(iv) adding energy to the pre-suspension to form particles having an average effective particle size of from about 400 nm to about 2 microns.

72. The method of claim 71 wherein the nonionic surfactant of the first

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surface modifier is selected from the group consisting of: polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

73. The method of claim 71 wherein the anionic surfactant of the first surface modifier is selected from the group consisting of: potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl glycerol, phosphatidyl inositol, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, bile acids and their salts and calcium carboxymethylcellulose.

74. The method of claim 71 wherein the cationic surfactant of the first surface modifier is selected from the group consisting of quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride.

75. The method of claim 71 wherein the first solvent is N-methyl-2-pyrrolidinone.

76. The method of claim 75 wherein the first surface modifier is a copolymer of oxyethylene and oxypropylene.

77. The method of claim 76 wherein the copolymer of oxyethylene and oxypropylene is a block copolymer.

78. The method of claim 71 further comprising the step of mixing into the solution a second surface modifier.

79. The method of claim 71 further comprising the step of:
mixing into the second solvent a third surface modifier selected from the group consisting of: anionic surfactants, cationic surfactants and nonionic surfactants.

80. The method of claim 79 wherein the third surface modifier is a nonionic surfactant selected from the group consisting of: polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and

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polyvinylpyrrolidone.

81. The method of claim 79 wherein the third surface modifier is an anionic surfactant selected from the group consisting of: potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl glycerol, phosphatidyl inositol, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, bile acids and their salts and calcium carboxymethylcellulose.

82. The method of claim 79 wherein the third surface modifier is a cationic surfactant selected from the group consisting of quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride.

83. The method of claim 79 wherein the first solvent is N-methyl-2-pyrrolidinone.

84. The method of claim 75 wherein the second surface modifier is a copolymer of oxyethylene and oxypropylene.

85. The method of claim 84 wherein the copolymer of oxyethylene and oxypropylene is a block copolymer.

86. The method of claim 79 further comprising the step of mixing into the solution a fourth surface modifier selected from the group consisting of: anionic surfactants, cationic surfactants and nonionic surfactants.

87. The method of claim 71 further comprising the step of: mixing into the second solvent a phospholipid.

88. The method of claim 87 wherein the phospholipid is selected from natural phospholipids and synthetic phospholipids.

89. The method of claim 87 wherein the phospholipid is selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, egg phospholipid and soybean phospholipid.

90. The method of claim 87 further comprising the step of mixing into the solution a fifth surface modifier selected from anionic surfactants, cationic surfactants and non-ionic surfactants.

91. The method of claim 90 wherein the nonionic surfactant of the fifth surface modifier is selected from the group consisting of: polyoxyethylene fatty alcohol

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ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

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92. The method of claim 90 wherein the anionic surfactant of the fifth surface modifier is selected from the group consisting of: potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl glycerol, phosphatidyl inositol, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, bile acids and their salts and calcium carboxymethylcellulose.

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93. The method of claim 90 wherein the cationic surfactant of the fifth surface modifier is selected from the group consisting of quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride.

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94. The method of claim 90 wherein the fifth surface modifier is bile acids and their salts.

95. The method of claim 90 wherein the first solvent is N-methyl-2-pyrrolidinone.

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96. The method of claim 95 wherein the energy-addition step comprises the step of:

subjecting the pre-suspension to heating, sonication, homogenization, counter current flow homogenization or microfluidization.

97. The method of claim 96 wherein the energy-addition step further comprises the step of subjecting the pre-suspension to heat.

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98. The method of claim 96 further comprising the step of removing solvent and excess surfactants through repeated removal and replacement of the supernatant fluid.

99. The method of claim 98 wherein the solvent and surfactant removal step is accomplished via centrifugation, diafiltration, force-field fractionation, or high-pressure filtration.

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